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Interrelationships among Zinc, Copper, Lead, and Cadmium in Food, Feces, and Organs of Humans

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Concentrations of zinc, copper, lead, and cadmium were determined in 20 samples of food collected over a period of 20 days, 221 samples of feces collected over a period of 5 days from 19 males, 17 females, and 11 children and 85 samples each of renal cortex and liver from autopsied human cadavers in order to investigate the relationships among the four metals and among the various matrices. In food the highest correlation was observed between copper and zinc (0.34). In feces the highest correlation was also between copper and zinc (0.45). In the liver the highest correlation was between cadmium and zinc (0.33), but that in the renal cortex was between copper and cadmium (0.52). These findings suggest that the relationships among the concentrations of the four metals in food and feces are almost equal to each other, but differ greatly from the concentrations in human organs due to the differing metabolic actions of the metals once they are absorbed into the body. In addition, it was observed that zinc and cadmium concentrations in the renal cortex increase with age, but copper and lead concentrations do not show much variation with age.

Introduction

Concentrations of heavy metals such as zinc, copper, lead, and cadmium in human tissues and organs as well as in foods have been studied by many authors (*1–4*). Interactions between two metals in animal experiments, e.g., cadmium and zinc or methylmercury and selenium, have also been well documented (*5, 6*). The findings from these studies are very important for a better understanding of the toxicokinetics of metals. However, these animal studies used unusually high doses of metals, much higher than any exposure (including occupational exposure) to which humans would be subjected. In addition, rather few studies have been carried out on the concentrations of zinc, copper, lead, and cadmium in human feces. The present study is designed to determine and evaluate the dynamics of these four trace elements, two of which are essential and two nonessential, in the organs, food, and feces of humans who have not been subjected to unusually high exposures of these metals. The working hypotheses were (1) whether accumulation and magnification in a particular organ or tissue occurred because of the different metabolism of each metal or possible interactions between metals, and (2) whether the ratios of these four metals in food changed during ingestion, resulting in different compositions in feces. The study aims to provide some background information on the ratios of the four metals in these media even though the samples of food, feces, and organs were not collected from the same individuals. There is no doubt that much work needs to be done on these hypotheses in the future.

Materials and Methods

Organ Study

The concentrations of the four metals in the renal cortex and liver were determined in a total of 85 cases (male and female) autopsied by coroners of the Keio University Department of Legal Medicine. These cases were sudden death victims without chronic diseases or chemical poisoning. The organ samples were digested by wet ashing and the concentrations of the four metals were determined by atomic absorption spectrophotometry after DDTC-MIBK extraction. Since the methods of pretreatment for feces and organs were different,

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ten samples each of feces and organs were measured using each pretreatment method in order to cross-check the methods. No differences were found.

Food Study

For the food study, samples were provided by the administrative office of Keio University Hospital. The foods submitted for testing were from a regular hospital diet, and included beverages such as tea and milk. The three meals from each day were mixed and freeze dried, and then stored in plastic containers. The samples were collected for 20 days (20 samples, 60 meals). Ten grams dry weight were used for analysis and the analytical methods were the same as those used for feces described below. The weight of the food items for each day, total daily calories, proteins, fat, and carbohydrates were recorded.

Feces Study

The feces study was carried out on 19 male medical students at the Keio University School of Medicine (21–24 years old), 17 female nursing students at the same school (20–22 years old), and 11 children (3 months–5 years) of the staff of the Keio University School of Public Health and Preventive Medicine. Feces were collected daily for five days. Information concerning the diet on the day previous to feces collection, smoking and drinking habits, history of residence, and regular intake of medicinal drugs was obtained for reference purposes. Feces samples were collected in plastic bags, weighed, and immediately stored in a freezer. Frozen samples were then treated by a vacuum freeze dryer and weighed. Then 2-g portions were analyzed for zinc, copper, lead, and cadmium content. The freeze-dried samples were then ashed in an electric furnace at 400°C (36 hr) and diluted with 0.5*N* acid. Zinc was measured directly by atomic absorption spectrophotometry. Copper, cadmium, and lead were measured by atomic absorption spectrophotometry after extraction with DDTC-MIBK.

Results

Figure 1 shows the concentrations of zinc, copper, lead, and cadmium in the renal cortex according to age for both sexes. Cadmium increases sharply from 0 to 19 years of age, continuing with a gradual increase up to about 50 years of age, and leveling off thereafter. The zinc concentrations for the 0–9 year age group are rather high, whereas the cadmium concentrations for this same age group are

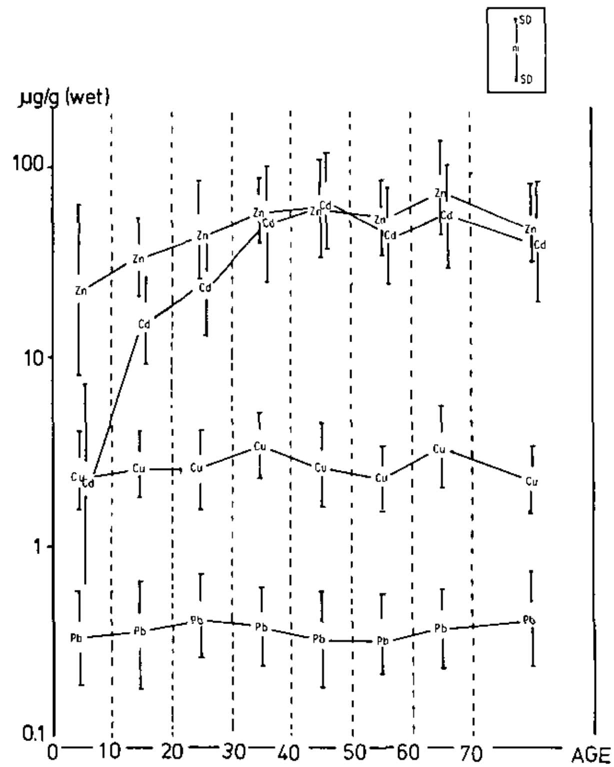

FIGURE 1. Concentrations of Zn, Cd, Cu and Pb in the renal cortex by age (both male and female).

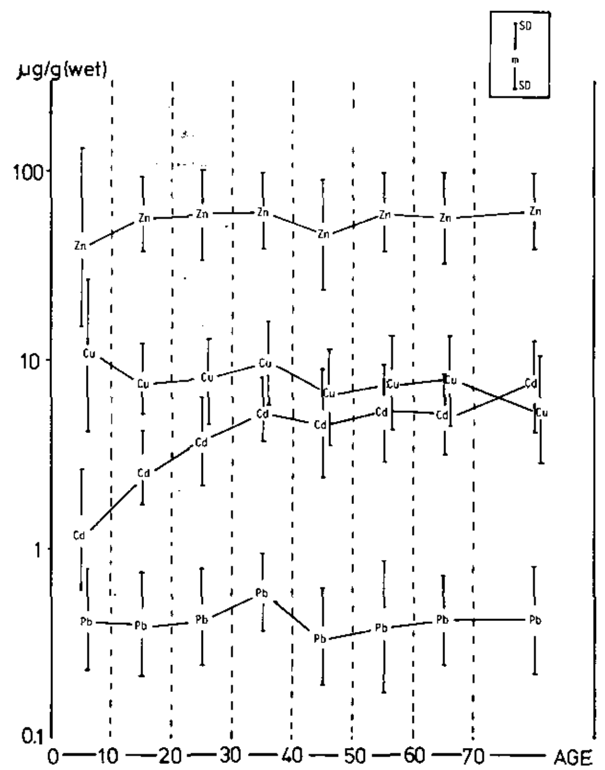

FIGURE 2. Concentrations of Zn, Cd, Cu and Pb in the liver by age (both male and female).

Table 1. Geometric mean and its range (mean × or ÷ s.d.) of the concentration of metals in liver and renal cortex.

Age	n	Metal concn in liver, μg/g				Metal concn in renal cortex, μg/g			
		Cd	Zn	Pb	Cu	Cd	Zn	Pb	Cu
0	6	0.74–1.41	33.91–1.40	0.32–1.41	15.21–2.85	0.69–1.45	17.43–1.19	0.25–1.72	2.36–1.15
1–9	9	1.63–2.29	65.01–1.53	0.47–1.65	9.02–2.30	4.43–2.76	38.78–1.87	0.34–1.33	2.68–1.12
10–19	6	2.65–1.60	57.20–1.20	0.39–1.78	8.05–1.22	15.11–1.57	33.42–1.33	0.35–1.80	2.75–1.17
20–29	16	3.67–1.72	56.25–1.56	0.42–1.66	7.73–1.46	23.29–1.49	47.16–1.65	0.41–1.44	2.50–1.38
30–39	4	5.39–1.46	62.72–1.26	0.59–1.30	9.34–1.40	53.03–1.95	56.99–1.11	0.38–1.31	3.59–1.15
40–49	19	4.61–1.93	45.82–1.80	0.34–1.69	6.12–1.62	68.65–1.64	61.47–1.64	0.32–1.63	2.75–1.46
50–59	4	5.11–1.82	60.58–1.31	0.38–2.21	7.46–1.64	42.79–1.59	55.83–1.19	0.34–1.32	2.31–1.11
60–69	10	5.01–1.66	56.81–1.54	0.41–1.45	7.68–1.52	54.74–1.72	72.43–1.64	0.37–1.31	3.31–1.40
70–	11	7.94–1.60	60.59–1.21	0.41–1.62	5.51–1.87	39.91–2.03	48.00–1.31	0.41–1.63	2.20–1.17

much lower. Both copper and lead show almost the same concentrations throughout all age groups. The lead level is the lowest among these four metals for all age groups.

Figure 2 shows approximately the same pattern of metal concentration levels in the liver as was found in the renal cortex, with the exception of copper. Copper shows the highest concentration in the liver in the 0–9-year age group, after which there is a slight decrease. The concentrations of copper in the liver are several times higher than in the renal cortex. There is not much difference in the zinc concentrations in the liver and renal cortex, but the cadmium concentrations in the renal cortex are almost 10 times higher than in the liver. Lead reveals almost the same concentrations in the liver as in the kidney. The numbers of samples, geometric means, and ranges of the concentrations shown in Figures 1 and 2 are summarized in Table 1.

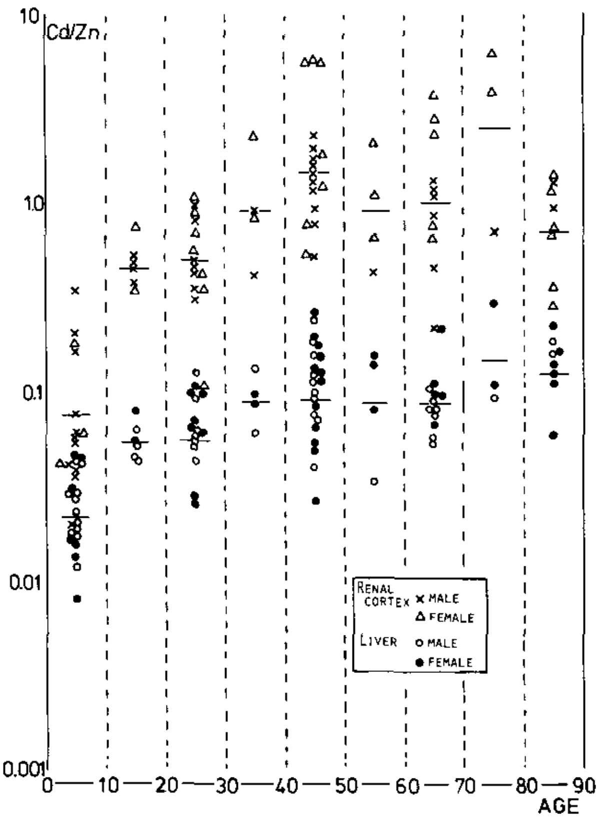

FIGURE 3. Cd/Zn ratio in the renal cortex and liver.

The Cd/Zn ratio in the renal cortex and the liver by sex and age is shown in Figure 3. The ratio in the renal cortex increases according to age up to the 40–49-year age group, after which it decreases. This pattern is very similar to the cadmium concentrations in the renal cortex by age group. The Cd/Zn ratio in the liver, on the other hand, seems to show no leveling off, but rather a sharp increase from the 0–9-year age group to the 10–19-year age group, with a very gradual increase thereafter according to age. The Cd/Cu ratio in two organs showed very similar patterns to the Cd/Zn ratio. However, the Cd/Cu ratio is ten times higher than the Cd/Zn ratio.

The Cd/Cu ratio in food, feces, and organs according to sex is shown in Figure 4. When this figure and Figure 5 are studied, it must be remembered that the food, feces, and organ samples were taken *from different individuals. It is very interesting to* note that the Cd/Cu ratio in food is almost equal to that in feces. However, the ratio in the organs is much higher than that in food or feces, being ten times higher in the liver and almost 100 times higher in the renal cortex.

Figure 5 shows the Cd/Zn ratio in food, feces, and organs. Again, the ratio in food and feces is the same, with a much higher ratio in the renal cortex and liver: almost 100 times higher in the kidney and 10 times higher in the liver. But the Cd/Zn ratio in food, feces, and organs is about 10 times lower than the Cd/Cu ratio in these three media.

Tables 2 through 5 show the correlations of concentrations of these four metals in food, feces, liver, and renal cortex respectively. As shown in Table 2, no significant correlation is observed between any two metals in food, most probably because of the small number of samples examined, although a rather high correlation is observed between copper and zinc, copper and cadmium, as well as copper and lead. Table 3 shows the correlations among the

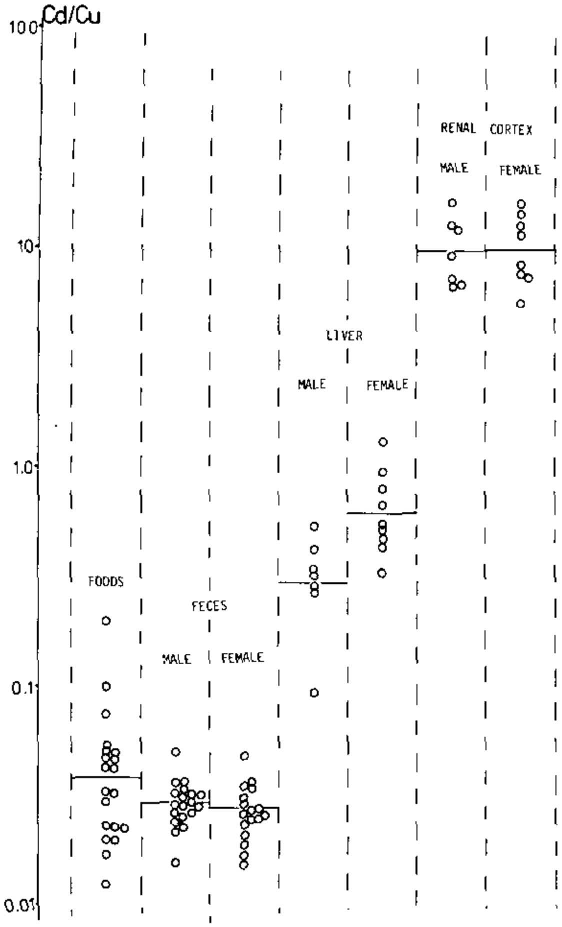

FIGURE 4. Cd/Cu ratio in foods, feces, and organs.

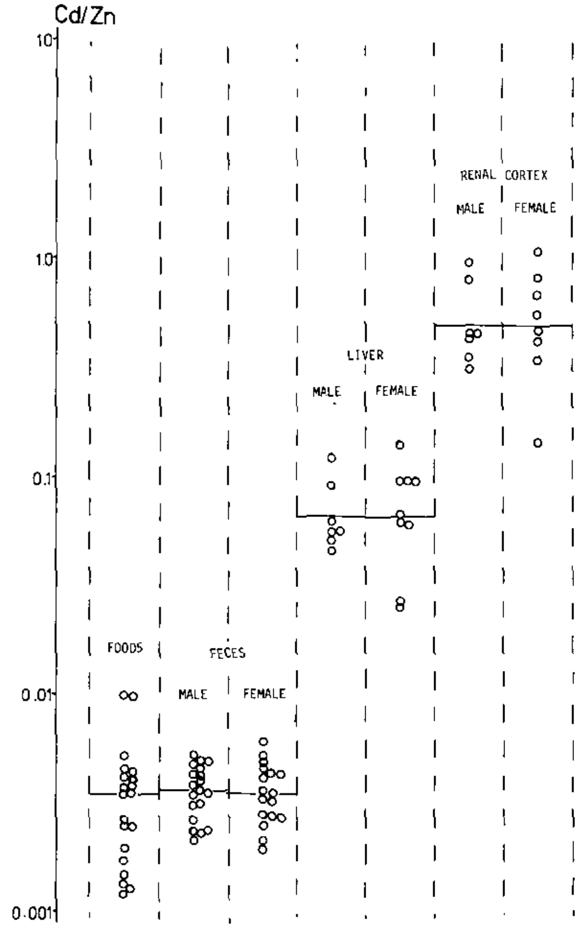

FIGURE 5. Cd/Zn ratio in foods, feces, and organs.

four metals in feces, indicating significant correlations for all paired combinations of the metals. The highest correlation (r = 0.45) was seen between copper and zinc, as is observed in food. It should be remembered that the correlation between cadmium and zinc is very low in both food and feces.

It is not surprising that correlations are seen among these metals in food and feces, because these are expressed by concentrations. But the purpose of this study was to discover which metals show the highest and lowest concentrations in food and feces and to study the relationships of these correlations in food and feces with those in the organs. When Tables 4 and 5 showing the correlations of these metals in the two organs are studied, a significantly high correlation between zinc and cadmium in the liver is seen but a reverse correlation appears between copper and cadmium, as well as a significant correlation between zinc and lead in the liver. There is also a significant correlation (r = 0.37) between cadmium and zinc in the renal cortex, as shown in Table 5. In addition, there are signifi-

Table 2. Correlations among cadmium, lead, copper, and zinc in food (n = 20).

	Cadmium	Lead	Copper	Zinc
Cadmium		0.122	0.287	−0.032
Lead	—		0.208	0.022
Copper	—	—		0.340
Zinc	—	—	—	

Table 3. Correlations among cadmium, lead, copper, and zinc in feces (n = 221).

	Cadmium	Lead	Copper	Zinc
Cadmium		0.174[a]	0.327[a]	0.134[b]
Lead	—		0.398[a]	0.382[a]
Copper	—	—		0.454[a]
Zinc	—	—	—	

[a] $p \leq 0.01$.
[b] $p \leq 0.05$.

Table 4. Correlations among cadmium, lead, copper, and zinc in liver ($n = 85$).

	Cadmium	Lead	Copper	Zinc
Cadmium		0.174	−0.137	0.330[a]
Lead	—		0.104	0.214[b]
Copper	—	—		0.091
Zinc	—	—	—	

[a] $p \leq 0.01$.
[b] $p \leq 0.05$.

Table 5. Correlations among cadmium, lead, copper, and zinc in renal cortex ($n = 85$).

	Cadmium	Lead	Copper	Zinc
Cadmium		0.083	0.522[a]	0.367[a]
Lead	—		0.118	0.143
Copper	—	—		0.381[a]
Zinc	—	—	—	

[a] $p \leq 0.01$.

cant correlations between copper and cadmium as well as copper and zinc in the renal cortex. However, no correlation is seen between lead and other metals in the renal cortex.

It was discovered from analyses of the data in these four tables that although correlations in food and feces were seen in almost all pairs of any two metals as expected, the correlations in the liver and renal cortex were quite different from those in food and feces. In particular, the correlation between zinc and cadmium in food and feces is quite low, whereas it was significantly high in the liver and renal cortex.

Table 6 shows the daily excretion in feces of the four metals in inhabitants of an area designated by the Japanese Ministry of Health and Welfare as requiring observation because of environmental pollution by cadmium, as well as in inhabitants of a control area and Tokyo. The daily excretion of cadmium in the polluted area is about 200 μg/day, even though the persons concerned were no longer consuming rice contaminated by cadmium. The cadmium excretion in the control area is 50 μg/day and in Tokyo is 40 μg/day. The daily excretion of lead is also very high in the polluted area, almost 230 μg, but in both the control area and in Tokyo, the daily excretion of lead is much lower than expected. It should also be noted that copper and zinc excretions are much higher in the polluted area than in the control area or in Tokyo.

Discussion and Conclusions

With regard to the concentrations of cadmium in the renal cortex and liver according to age, the present study indicates almost the same patterns as reported by Friberg et al. (*7*) and Tsuchiya, Seki, and Sugita (*8*), as well as by many other investigators. There are data on simultaneous determinations of zinc and cadmium (*11*) and lead and cadmium (*12*), but simultaneous determinations of copper and cadmium in the renal cortex and liver are not well documented. It is especially interesting to note that copper (an essential element) showed a higher level in the liver than cadmium and lead among all age groups. It is also important to note that the copper concentrations throughout all age groups are much higher in the liver than in the renal cortex and that lead concentrations in both the liver and renal cortex were lowest of all metals.

The Cd/Cu and Cd/Zn ratios in the renal cortex and liver increased sharply until about 20 years of age. In the renal cortex, the ratios level off by the age of about 50, and then decrease slightly in the very elderly (after 70 years). However, the ratios in the liver do not seem to level off, but continue to increase slightly by age. The Cd/Cu ratio was about ten times higher in the renal cortex and liver than the Cd/Zn ratio. The Cd/Zn ratio observed in this study was much higher than those reported by Schroeder et al. (*9*) from the U. S. and by Piscator and Lind (*10*) from Sweden. Both reported ratios of 0.6–0.7 and 0.5–0.6, respectively, for ages 35–55, while the present study indicated 0.9–1.1 for the same age group. This difference seems to depend not only on the fact that concentrations of cadmium are generally higher among Japanese than among

Table 6. Daily excretion of cadmium, lead, copper, and zinc in feces.

Male	Wet weight of feces, g	Dry weight of feces, g	Ratio dry/wet, %	Lead, μg/g dry (μg/day)	Cadmium, μg/g dry (μg/day)	Copper, mg/g dry (mg/day)	Zinc, mg/g dry (mg/day)
Polluted area 30 males (age > 50)	203.6 ± 53.2	52.6 ± 26.4	25.8 ± 10.4	4.01 ± 2.53 (225.6 ± 206.0)	5.10 ± 2.78 (197.6 ± 113.8)	0.05 ± 0.02 (2.71 ± 1.82)	0.42 ± 0.12 (21.61 ± 12.48)
Control area 30 males (age > 50)	174.5 ± 78.2	34.2 ± 13.3	21.2 ± 6.4	0.94 ± 0.73 (36.3 ± 32.5)	1.49 ± 1.32 (48.6 ± 41.9)	0.03 ± 0.02 (1.27 ± 0.73)	0.31 ± 0.08 (10.27 ± 4.73)
Tokyo inhabitants 19 males for 5 days (age 21–24)	116.2 ± 79.5	27.2 ± 17.3	23.4 ± 7.3	1.60 ± 0.60 (45.0 ± 26.0)	1.33 ± 0.58 (36.2 ± 31.2)	0.05 ± 0.02 (1.32 ± 0.91)	0.38 ± 0.14 (10.45 ± 6.48)

Americans or Swedes, but also on the fact that zinc is present at a higher level in the renal cortex of the Japanese.

It was also noted in this study that despite the fact that the same pattern of Cd/Cu and Cd/Zn ratios was noted in food and feces, both the ratios in the liver and renal cortex were greatly amplified, being about 10 times higher in the liver and 100 times higher in the renal cortex than in food and feces.

There were some correlations between all pairs of the metals in feces (221 samples) but no significant correlation in food, probably because there were only 20 samples. The correlation between zinc and cadmium in feces was rather low. However, there was a significant correlation ($r = 0.37$) between cadmium and zinc in the renal cortex, and a significant correlation ($r = 0.33$) between these same metals in the liver. It is very important to note that there was a significant correlation between copper and cadmium in the renal cortex. This may imply very close relationships between zinc and cadmium as well as copper and cadmium in the renal cortex, whereas no such relationship was noted between copper and cadmium in the liver.

The differences and interrelationships among metals in food, feces, and organs observed in this study show the need for further investigations, since it is difficult to explain the findings in this study from the viewpoint of the toxicokinetics of these four metals.

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